REMARKS/ARGUMENTS

A Terminal Disclaimer is provided herewith. The disclaimer addresses the Office Action's non-statutory double patenting rejection.

A substitute computer readable form (CRF) copy of the Sequence Listing, a substitute paper copy of the Sequence Listing, and statement to support Filings and Submissions in Accordance with 37 CFR §§ 1.821 – 1.825 are provided herewith. The substitute papers and CRF correct the previous Sequence Listing materials submitted April 20, 2004. In the previous materials, the amino acid sequence of SEQ ID NO: 1 was inadvertently truncated to 32 residues rather than the correct 37 residues. Also, residue 1 in SEQ ID NO: 1 is indicated as "Glu", but should be "Gln." Support for the substitute sequence for SEQ ID NO:1 is found in Fig. 1A. No other changes are made in the Sequence Listing.

A new title is provided, in keeping with the Examining Attorney's suggestion.

In the Preliminary Amendment filed with this utility patent application on February 27, 2004, and a second Preliminary Amendment submitted October 6, 2004, Applicants added and corrected, respectively, a Cross Reference to Related Applications section. The Cross Reference section is further amended in this paper to indicate that Application Serial No. 10/142,120 is now U.S. Patent No. 6,737,064.

The specification is also amended to add a Statement Regarding Federally Funded Research or Development.

In accordance with MPEP § 2001.06(b), the Examiner is respectfully requested to acknowledge that prior art submitted in the divisional and parent priority applications have been considered and reviewed in the current application.

Claims

Claims 1-27 are pending. Claims 6-19, 26 and 27 are currently withdrawn from consideration. In the February 27, 2004 Preliminary Amendment, claims 20-25 were canceled.

Claims 1 and 3 were previously amended in the February 27, 2004 Preliminary Amendment filed with this utility patent application. The current amendments are made with respect to the previously amended claims.

Claim 1 is amended to clarify that the fragment of interleukin-2 contains an amino acid sequence corresponding to residues 37-58 of SEQ ID NO: 3. Support is found throughout the specification, for example, at page 10, lines 14-27.

Claim 1 is also amended to clarify that the cytokine activity is interleukin-2 cytokine activity.

Claim 4 is amended to clarify that the peptide consists essentially of residues 1-37 of SEQ ID NO: 1.

Claim 5 is amended to clarify that the peptide includes a cysteine residue, and the peptide is capable of forming a dimer through a disulfide bridge.

Rejection under 35 U.S.C. § 112 - Descriptiveness

The rejection of claims 1-5 under 35 U.S.C. § 112, first paragraph, as lacking descriptive support in the specification is respectfully traversed. As amended, claims 1-5 call for a fragment of interleukin-2 containing an amino acid sequence corresponding to residues 37-58 of SEQ ID NO: 3. The specification provides a description fully supporting the amended claims.

The specification describes interleukin-2 ("IL-2") generally as an important biological mediator in both animals and man (page 3, lines 1-4), and as possessing both cytokine activity and vascular permeability activity. Moreover, the specification describes the structure of IL-2 as comprising four major amphipathic alpha helices, and describes IL-2's structural similarity to other cytokines (page 2, line 35 – page 3, line 20). The specification further indicates that peptides containing amino acids 37-58 of human IL-2, including peptides containing residues 22-58, 33-58 and 37-72, all enhance vasopermeability (Examples 7 and 8). The specification also cites references which indicate that, since at least 1992, it was known in the art that the amino acid sequence and the overall structure of IL-2 were highly conserved among animal species [see the publications of J.F. Bazan, Science, vol. 257, p. 410-412 (1992), and D.B. McKay, Science, vol. 257, p. 412-413 (1992), cited on page 3, lines 25-30 of the specification].

A copy of the cited Bazan publication and McKay publication are provided herewith for the Examiner's convenience. Both publications were previously provided with IDS submissions in the claimed priority applications. Fig. 2 of the Bazan publication shows an alignment of the amino acid sequences of IL-2 from a number of animal species – mouse, rat, bovine, sheep, pig and human. As shown in the alignment, IL-2 from these representative species is highly conserved. Indeed, in comparing the various amino acid sequences corresponding to amino acids 22-58 of IL-2 from these representative species, over 50% (19/37) of the amino acid positions are identical, with the remaining positions containing conservative substitutions. Not only is the amino acid sequence highly conserved from residues 22-58, but the overall structure of this region is also highly conserved among species. This structural conservation is reflected by the presence of Helix A, a short helical segment α, a β-strand, an A-B loop, and Helix B in the region corresponding to amino acids 22-58 of each animal species (see Fig. 2, line marked "MODEL struc"). The McKay publication supports the overall structure presented by Bazan.

Considering the information provided in the specification and the knowledge present in the art well before the 1996 filing date of the current application's parent application, the specification readily meets the written description requirement. The specification describes the vasopermeability enhancing ability of peptides containing residues 22-58, 33-58, 37-58, and 37-72 of human IL-2. These portions of IL-2 as well as the entire region from residues 22-58 were well known to be highly conserved, based on sequence alignments and modeling of IL-2 sequences from a number of animal species. Thus, a person skilled in the art would readily

recognize that the vasopermeability enhancing activity of residues 22-58 of human IL-2 would also apply to the corresponding region of highly conserved IL-2 molecules of other animal species. Moreover, the IL-2 sequence alignments readily identify which amino acids are constant, which amino acids are variable, and the kinds of substitutions to make. In all, the specification combined with the knowledge in the art provides a complete description of the variety of vasoactive peptides encompassed by residues 22-58 of IL-2.

The specification conveys to those skilled in the art the full scope of the subject matter of amended claims 1-5. As such, the application more than satisfies the written description requirement.

Rejection under 35 U.S.C. § 112 – Enablement

The rejection of claims 1-5 under 35 U.S.C. § 112, first paragraph, as non-enabled is respectfully traversed. The test of enablement is whether a person skilled in the art could make or use the invention without undue experimentation, based upon the disclosures in the patent and information known in the art." MPEP § 2164.01. In the present case, the claims are fully enabled.

As noted above, the specification describes the vasopermeability enhancing ability of peptides containing residues 22-58, 33-58, 37-58, and 37-72 of human IL-2. These portions of IL-2 as well as the entire region from residues 22-58 were well known to be highly conserved among animal species. A person skilled in the art would therefore readily recognize that the vasopermeability enhancing activity of residues 22-58 of human IL-2 would also apply to the corresponding region of highly conserved IL-2 molecules of other animal species. Moreover, IL-2 sequence alignments well-known in the art readily identify which amino acids are constant, which amino acids are variable, and the kinds of substitutions to make. This knowledge combined with the vasopermeability assays described in the specification are more than enough to design peptides consisting essentially of residues 27-58 of SEQ ID NO: 3 without undue experimentation. In all, the specification combined with the knowledge in the art completely enables the variety of vasoactive peptides encompassed by the claims.

By clarifying that claims 1-5 are directed to fragments of IL-2 which contain amino acid sequences corresponding to residues 37-58 of SEQ ID NO: 3, it is apparent that the claims are not directed to just any vasoactive peptide of IL-2. Thus, claims 1-5 encompass discreet vasoactive peptides comprising fragments of IL-2, and are not in any way similar to single means claims.

The specification conveys to those skilled in the art how to make and use the invention commensurate with the full scope of the subject matter of amended claims 1-5. As such, the application more than satisfies the enablement requirement.

Rejection under 35 U.S.C. § 112 - Indefiniteness

The rejection of claims 1-5 under 35 U.S.C. § 112, second paragraph, as indefinite is respectfully traversed.

Amended claim 1 recites "substantially free of interleukin-2 cytokine activity," which makes clear what cytokine activity the claim refers to.

The specification and the knowledge in the prior art fully describe and enable claims to different animal species of IL-2, not just to human IL-2. Because different species of IL-2 are appropriately claimed, claim 1 is definite.

The specification and the knowledge in the art fully describe and enable claims to various vasoactive peptides containing residues 37-58 of SEQ ID NO:3, or residues 1-37 of SEQ ID NO: 1. Therefore, the inclusion of "essentially of" in the claims is appropriate and not indefinite.

The February 6, 2004 amendment to claim 3 and the current amendment to claim 4 clarify the subject matter of the claims.

The amendment to claim 5 clarifies that the peptide is capable of forming a dimer.

In view of the foregoing amendments and remarks, Applicants submit that the present application is in condition for allowance. A Notice of Allowance is therefore respectfully requested.

The fee for a 1 month extension of time is submitted herewith.

No other fee is believed due. However, the Commissioner is hereby authorized during prosecution of this application and any related appeal, to charge any fees that may be required (except for patent issue fees required under 37 CFR §1.18) or to credit any overpayment of fees to Deposit Account No. 50-0337. If an additional extension of time is required in connection with this paper, please consider this a Petition therefor and charge any fees required to Deposit Account No. 50-0337.

Dated: 12/21/06

Respectfully submitted,

Miles Yamanaka
Reg. No. 45,665

FULBRIGHT & JAWORSKI L.L.P
555 South Flower Street , 41st Floor
Los Angeles, CA 90071
(213) 892-9200 – Telephone
(213) 892-9494 – Facsimile

Attachments: Terminal Disclaimer
Paper copy of the Sequence Listing
Statement to support Filings and Submissions under 37 CFR §§ 1.821 – 1.825

Paper - J.F. Bazan, Science, vol. 257, p. 410-412 (1992)

Paper - D.B. McKay, Science, vol. 257, p. 412-413 (1992)

Enclosure: Computer readable copy of the Sequence Listing (diskette)